

## CLINICAL GUIDANCE

# Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients

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## INTRODUCTION

Large numbers of individuals who have been infected with SARS-CoV-2, the virus responsible for COVID-19, continue to experience a constellation of symptoms long past the time that they have recovered from the acute stages of their illness. Often referred to as “long COVID,” these symptoms, which can include fatigue, shortness of breath, palpitations, cognitive dysfunction (“brain fog”), sleep disorders, fevers, gastrointestinal symptoms, anxiety, depression, and others, can persist for months and can range from mild to incapacitating. Although still being defined, these effects can be collectively referred to as postacute sequelae of SARS-CoV-2 infection (PASC).<sup>1</sup> The magnitude of this problem is not

yet known, but given the millions of individuals worldwide who have had, or will have, COVID-19, the societal impacts are likely to be profound and long lasting.<sup>2-5</sup>

It is widely acknowledged that systematic study is needed to develop an evidence-based approach for caring for patients with PASC. At present, there is a dearth of rigorous scientific evidence regarding effective assessment and treatment of PASC that prevents the creation of evidence-based clinical guidelines. However, the U.S. health system is currently seeing an increase in the number of patients presenting with PASC, and there is an urgent need for clinical guidance in treating these patients. The goal of this, and future statements, is to provide practical guidance to clinicians in the assessment and treatment of patients presenting with PASC.

This Consensus Guidance Statement on fatigue is the first of a series focused on the most prominent PASC symptoms.

## PASC consensus guidance statement methods

The American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary PASC Collaborative (“PASC Collaborative”) was created, in part, to develop expert recommendations and guidance from established PASC centers with extensive experience in managing patients with PASC. The PASC Collaborative is following an iterative, development approach to achieve consensus on assessment and treatment recommendations for a series of Consensus Guidance Statements focused on the most prominent PASC symptoms. These statements were developed by a diverse team of experts, with input from patient representatives with a history of PASC, and integrate current experience and expertise with available evidence to provide tools to clinicians treating patients. There is an intentional focus on health equity as disparities in care and outcomes are critically important to address. Beyond patient care, the hope is that a broadened understanding of current patient care practices will help identify areas of future research. A full description of the methodology is also published in this issue.<sup>6</sup>

We acknowledge that the definition of PASC is evolving, and there are various factors that contribute to diagnosis. The PASC Collaborative sought input from patient representatives with a history of PASC and patient-led research initiatives to inform recommendations. For example, previous literature has suggested that PASC be defined as the continuation of symptoms beyond 3 or 4 weeks from the onset of acute infection.<sup>7</sup> Other definitions of PASC include symptoms lasting longer than 3 months.<sup>8</sup> Based on feedback of patient representatives that earlier evaluation, diagnosis, and management can improve access to beneficial interventions, for the purpose of this Consensus Guidance Statement, we recommend expanded assessment if symptoms are not improving 1 month after acute symptom onset.

These Consensus Guidance Statements are intended to reflect current practice in patient assessment, testing, and treatments. They should not preclude clinical judgment and must be applied in the context of the specific patient, with adjustments for patient preferences, comorbidities, and other factors.

## Fatigue in individuals with PASC

Fatigue is a feeling of weariness, tiredness, or lack of energy. It can be physical, cognitive, or emotional, mild to severe, intermittent to persistent, and affect a person’s

energy, motivation, and concentration. Fatigue can negatively affect an individual’s sense of well-being and quality of life and generally lacks objective markers. Fatigue during an acute viral illness is common; however individuals with PASC are often presenting with long lasting and debilitating fatigue after recovery from their acute viral illness.<sup>5</sup> Further discussion on the definition and impact of fatigue can be found in the Institute of Medicine’s 2015 report on chronic fatigue syndrome (Chapter 4).<sup>9</sup>

Individuals are seeking care from their clinicians for fatigue following COVID-19. Among nonhospitalized adults with a history of COVID-19 and enrolled in an integrated health system in Georgia, approximately two thirds had at least one outpatient medical encounter between 1 and 6 months after their diagnosis.<sup>10</sup> Approximately two thirds of these patients received a new primary diagnosis, with fatigue being one of the most common based on *International Classification of Diseases, Tenth Revision* codes.<sup>10</sup>

In another study describing the long-term health consequences for individuals hospitalized with COVID-19, the most common symptoms were fatigue or muscle weakness (63%) and sleep difficulties (26%).<sup>11</sup> Anxiety and depression were also common, reported by 23% of patients. Greater than 20% of patients had performances on the 6-minute walk test below the lower-limit of normal.<sup>11</sup>

The Patient Led Research Collaborative, a self-organized group of individuals with PASC who conduct patient-led research around the long COVID experience, conducted a study of self-reported symptoms of individuals enrolled in support groups for PASC.<sup>12</sup> A majority (96%) of individuals who completed the survey self-identified as having PASC reported symptoms beyond 90 days. The most common early symptoms were fatigue, cough, shortness of breath, headaches, muscle aches, chest tightness, and sore throat. The most frequent symptoms reported after 6 months were fatigue, postexertional malaise, and cognitive dysfunction. Greater than 85% of individuals experienced relapses of their symptoms, with exercise, physical or mental activity, and stress being the main triggers. In addition, 42.5% reported requiring a reduced work schedule compared to pre-illness and 22.3% were not working at the time of survey because of their health conditions.<sup>12</sup>

## PASC FATIGUE PRESENTATION AND ASSESSMENT RECOMMENDATIONS

Fatigue is among the most common persistent symptoms following COVID-19 in both individuals that have been hospitalized ( $p = 24.6\%$ , confidence interval [CI] 20.11-29.72) and those that have not been hospitalized ( $p = 37.1\%$ , CI 26.54-49.06).<sup>13</sup> Although fatigue likely improves over time, it can persist beyond 6 months.<sup>2,5,7</sup>

As noted in the PASC Collaborative methodology,<sup>6</sup> the recommendations that follow are based on expert

consensus. Specific guidance recommendations that have been approved by consensus will be noted in the tables and recommendations will be followed by additional discussion (Table 1).

## Fatigue assessment recommendation statements discussion

It is not unusual for individuals to have persistent and fluctuating fatigue during their recovery from acute COVID-19 disease, particularly in the first 1 to 2 months. This fatigue can involve both physical and cognitive components. This document focuses on physical fatigue and a subsequent Consensus Guidance Statement will focus on cognitive issues. Additional assessment and management of post-COVID fatigue should be considered if a patient is not continuing to improve after the initial 4 weeks beyond symptom onset, if symptoms are severe, or if the patient is experiencing negative impacts on quality of life. In cases of mild fatigue that is not functionally limiting, it can be monitored for improvement as part of the natural recovery from COVID-19.

Common descriptions of PASC-related fatigue include:

- Severe exhaustion after minimal physical or mental exertion

- The sense of being weighed down all day
- After having a “good day” of increased activity level, the feeling of “crashing” requiring several days of recovery
- Persistent tiredness or exhaustion after sleep/upon waking

A wide differential for central and contributing factors to PASC-related fatigue should be considered (Table 2). This differential may be affected by the severity of initial illness with those critically ill being at risk for post-intensive care syndrome (PICS). Potential contributions to PICS-related fatigue include circadian rhythm disorders, critical illness polyneuropathy and myopathy, and mood disorders.<sup>14-16</sup> Pregnant women, racial/ethnic minority individuals, and other vulnerable populations may be at higher risk for serious COVID-19 related illness and subsequent PICS (See Appendix: Health Equity Considerations and Examples in Post-Acute Sequelae of SARS-CoV-2 Infection [PASC]: Fatigue).<sup>17</sup>

In patients presenting with fatigue, it is important to consider the evaluation of fatigue and diminished activity tolerance as related but distinct conditions. As these two symptoms may intersect, the differential etiologies of fatigue should be considered in conjunction with a separate differential for lowered activity tolerance.

**TABLE 1** PASC fatigue assessment recommendations

#	Statement
1	Patients should be assessed for fatigue patterns throughout their normal day to guide activity recommendations.
1a	Patients should be assessed for their responses to initiating and escalating activity on their fatigue.
1b	Patients should be evaluated for changes in daily functioning and activity levels.
1c	Patients' physical functioning and endurance should be assessed to inform activity and therapy recommendations. (Examples of tests that can be chosen based on an individual's activity tolerance: 30 s sit to stand <sup>55</sup> ; 2-min step (seated or standing) <sup>56</sup> ; 6 min walk test <sup>57</sup> ; 10 m walk test <sup>58</sup> ).
2	Clinicians should assess for changes in activities of daily living, independent activities of daily living, school, work, and avocational (ie, hobbies)
3	A full patient history with review of preexisting conditions should be conducted
4	Patients should be evaluated for conditions that may exacerbate fatigue symptoms and warrant further testing and potential subspecialty referral (see Table 2). Particular areas include: <ul style="list-style-type: none"> <li>• Sleep</li> <li>• Mood, including anxiety, depression and PTSD. Note: Patients often report dissatisfaction with their care because of their persistent symptoms being attributed to psychological factors. It is important to note that mood disorders may be secondary to persistent medical issues or one of many factors leading to fatigue.</li> <li>• Cardiopulmonary</li> <li>• Autoimmune</li> <li>• Endocrine</li> </ul>
5	A medication review should be conducted to investigate medications that may be contributing to fatigue. Of note, antihistamine, anticholinergic, and antidepressant/anxiolytic medications can contribute to fatigue in patients with PASC.
6	The following basic lab workup should be considered in new patients or those without lab workup in the 3 months before visit including complete blood count with differential, chemistries including renal and hepatic function tests, thyroid stimulating hormone, c-reactive protein or erythrocyte sedimentation rate, and creatinine kinase. Other laboratory tests may be considered based on the results of these tests or if there is specific concern for comorbid conditions as outlined in Table 2.

When evaluating the etiology of fatigue, the following should be considered as central or contributing factors: sleep disorders, endocrine disorders, nutritional disorders, chronic infectious disorders, autoimmune/inflammatory disorders, cardiac disorders, respiratory disorders, psychiatric disorders, malignancies, drug reactions, and adult-onset metabolic disorders (See Table 2).

Diminished activity tolerance is the inability or reduced ability to perform physical activity at the normally expected frequency, intensity level, or duration for people of that age, size, gender, and muscle mass. Individuals may experience unusually severe post-exercise pain, fatigue, nausea, vomiting, or other negative effects. When evaluating the etiology of diminished activity tolerance, the following disorders or system dysfunctions should be considered as central or contributing factors: pulmonary, cardiovascular, and/or neuromuscular systems.

The presentation of fatigue in individuals with PASC may appear similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). ME/CFS is a complex syndrome that often occurs following viral illness. A 2015 Institute of Medicine report on ME/CFS created specific diagnostic criteria as outlined in Table 3.<sup>9</sup>

The specific pathophysiology behind ME/CFS has yet to be discovered. The Centers for Disease Control and Prevention has developed treatment recommendations for ME/CFS that have been used to help develop the current treatment recommendations for PASC-related fatigue.<sup>18</sup> However, more data are needed to understand if and in which individuals PASC-related fatigue is a manifestation of ME/CFS and in which individuals PASC-related fatigue represents a distinct process.

Finally, it is important to note that the etiology of fatigue may be multifactorial in individuals with PASC and there may not be one unifying cause of PASC-related fatigue.

## PASC FATIGUE TREATMENT RECOMMENDATIONS

### Fatigue treatment recommendation statements discussion

As with any treatment plan, clinicians treating patients with PASC-related fatigue are encouraged to discuss the unknowns of PASC treatments, as well as the pros and cons of any therapeutic approach. It may also be helpful to discuss that despite the unknown time course of post-COVID symptoms, it is the experience of established PASC centers that fatigue tends to slowly improve over time. As treatment is initiated, patients should be followed for their response to treatment and impact of treatment on level of function.

As with the PASC patient assessment, therapeutic options vary and should be customized based on history,

comorbidities, and treatment response to date. It is important to note that if specific etiologies of fatigue are identified (see Table 2), they should be addressed as part of the treatment plan (Table 4, Recommendation #4).

The current recommendations are based on the experience of the PASC Collaborative clinics and have helped to alleviate symptoms in cases in which specific contributing etiologies have not been identified or, despite addressing, symptoms persist. Additional details on techniques used by clinicians are summarized next. As treatment efficacy of therapeutic options emerges, these recommendations will be reviewed and revised on a periodic basis.

### Begin an individualized and structured phased return to activity program

An individually titrated, symptom-guided program of return to activity is recommended for patients presenting with fatigue. The goal of a rehabilitation program is to restore patients to previous levels of activity and improve quality of life. Until those goals have been achieved, the rehabilitation program should not focus on high intensity aerobic exercises or heavy weightlifting to build strength and endurance. If the rehabilitation program is advanced too quickly or is too intense, it may worsen symptoms and lead to postexertional malaise (PEM), a diagnostic criterion of ME/CFS.<sup>9</sup>

The titrated approach encourages patients to perform activities at a submaximal level to avoid exacerbation of fatigue and PEM. Activity should be adjusted in response to symptoms that develop during or after activity. Before starting this program, it is crucial for the clinician to educate the patient on recognizing perceived exertion and the use of other metrics such as heart rate or exertion scales (such as the Borg Rating of Perceived Exertion Scale) that can guide the individual toward submaximal exertional activities. Smartphones and activity trackers may also be effective methods to monitor duration and intensity of activity.<sup>19</sup>

The severity of PASC fatigue can range from mild to severe. Most patients with PASC who have presented to the multidisciplinary clinics report moderate to severe symptoms. There are multiple well-validated measures available to measure fatigue such as the Fatigue Severity Scale, the Fatigue Impact Scale, and the Brief Fatigue Impact Score.<sup>20</sup> Previous literature has defined levels of fatigue in cancer patients on a 10-point scale from 0 (“not present”) to 10 (“as bad as you can imagine”) with scores of 1–3 representing mild fatigue, 4–6 representing moderate fatigue, and 7–10 representing severe fatigue.<sup>21</sup> In the context of ME/CFS, the National Institute for Health and Care Excellence in their 2007 guidelines define severity of fatigue.<sup>22</sup> Based on our experience, we find these definitions appropriate

**TABLE 2** Common PASC system manifestations, symptoms, additional testing/studies and referral options

	Cardiovascular	Pulmonary	Endocrine	Autoimmune	Mood disorders	Sleep disorders
Common Symptoms and Signs	<p><b>Symptoms:</b> Chest pains, palpitations, sweating, nausea, fatigue, leg swelling, shortness of breath - at rest/on exertion/lying flat/waking up at night, dizziness on standing, feeling faint/fainting</p> <p><b>Signs:</b> Pallor, tachypnea, tachycardia, diaphoresis, pulmonary rales, lower extremity edema, hypotensive sitting/standing - orthostatic, presyncopal/syncopal, poor activity tolerance/endurance</p>	<p><b>Symptoms:</b> Shortness of breath – at rest/ on exertion, cough, wheeze, fatigue, poor activity tolerance</p> <p><b>Signs:</b> Tachypnea, tachycardia, cough, hypoxia/low pulse oximeter, pulmonary wheezes/rhonchi/“Velcro” rales, poor activity tolerance/endurance</p>	<p><b>Symptoms:</b> Palpitations, fatigue, dizziness, weight gain/loss, sense of chills/fever, irregular menstrual cycle, poor diabetic control, excessive thirst/urination</p> <p><b>Signs:</b> Tachycardia, poor activity tolerance, weight gain/loss, low/elevated temperature, elevated finger-stick/urine glucose, ketotic (fruity) breath</p>	<p><b>Symptoms:</b> Rash, joint/muscle pain and stiffness, fever, mouth sores/ulcers, cold/pale/blue/red fingers, sharp chest pain, numbness/tingling/burning in fingers/toes, blurry/decreased vision</p> <p><b>Signs:</b> Rash, arthropathy – swelling/warmth/decreased ROM, myopathy – tenderness/weakness, fever, Raynaud’s phenomena, pleuritic pain on deep breathing, altered sensation, decreased visual acuity</p>	<p><b>Symptoms:</b> Anxiety, irritability, chest tightness, low frustration tolerance, depression, fatigue, mood swings, palpitations, change in memory/recall</p> <p><b>Signs:</b> flat affect/low mood, emotional lability that is, crying/laughing inappropriately, limited impulse control, psychosis</p>	<p><b>Symptoms:</b> Poor sleep - hard to fall asleep/wakes frequently/wakes early, nonrestorative/refreshing sleep - “tired” on waking, snoring, frequent urination at night, bad dreams/nightmares, falls asleep during the day, morning headaches</p> <p><b>Signs:</b> Snoring, restless legs, observed apneic episodes, hypertension, arrhythmias, narcolepsy, congestive heart failure, impaired neurocognition, poorly controlled mood disorder</p>
Further Studies to Consider in Addition to Basic Laboratory Evaluation	<p>B-type natriuretic peptide (BNP), troponins, D-dimer, chest-x-ray (CXR), electrocardiogram (EKG), echocardiogram (ECHO), exercise stress test/ cardiopulmonary exercise test (EST/CPET), Holter monitor, cardiac magnetic resonance imaging</p>	<p>D-dimer, pulmonary function tests (PFTs), CXR, computed tomography (CT) chest (with contrast if concerned for a pulmonary embolism)</p>	<p>Thyroid stimulating hormone (TSH)/ Free T4 (thyroxine), cortisol levels, growth hormone, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (men), estradiol (women)</p>	<p>Imaging of effected joints, antibody screen based on ongoing symptoms</p>	<p>An anxiety and depression screen (for example, the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI) fast screen; Patient Health Questionnaire (PHQ)-2/9, Geriatric Depression Scale (GDS)</p>	<p>Sleep apnea screen (eg, the STOP-BANG questionnaire or Epworth Sleepiness Scale [ESS]) overnight sleep study for oximetry and sleep apnea</p>
Referral	Cardiology	Pulmonology	Endocrinology	Rheumatology	Psychiatry	Sleep Medicine

Abbreviations: PASC, postacute sequelae of SARS-CoV-2 infection; ROM, range of motion.

as a basis for the following classification of PASC-related fatigue.

- **Mild fatigue:** Individuals have intact mobility, can perform activities of daily living and do light housework (often with difficulty). They are also able to continue working or going to school but may have stopped other, nonessential activities. They often take time off, require modifications to their schedule, and use weekends to recover from their work week.
- **Moderate fatigue:** Individuals have decreased community mobility and are limited in their performance of instrumental activities of daily living (particularly preparing meals, shopping, doing laundry, using transportation, and performing housework). They require frequent rest periods and naps and have generally stopped work or school.
- **Severe fatigue:** Individuals are mostly confined to the home and may have difficulty with activities of daily living (eating, bathing, dressing, transferring, toileting, mobility). Leaving the home for these individuals is very limited and often leads to prolonged/severe after-effects.

**TABLE 3** National Academy of Sciences proposed diagnostic criteria for ME/CFS

Proposed Diagnostic Criteria for ME/CFS
Diagnosis requires that the patient has the following three symptoms:
1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, education, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest,
2. Postexertional malaise <sup>a</sup> and
3. Unrefreshing sleep <sup>a</sup>
At least one of the following manifestations is also required:
1. Cognitive impairment <sup>†</sup> or
2. Orthostatic intolerance

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<sup>a</sup>Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

Abbreviation: ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome.

The recommended program depends on the severity of PASC-related fatigue:

- **Mild fatigue:** We advise patients to continue all household and community activities that have been tolerated with a slow return to higher intensity activities and exercise following the “rule of tens.” The “rule of tens” consists of increasing duration, intensity, and frequency of activity/exercise by 10% every 10 days. Using the Rate of Perceived Exertion (RPE) scale, start at RPE 10–11/Light and progressing to 14–15/Hard on resumption of exercise. If patients do not feel comfortable with initiating this program or if gentle resumption of physical activities has previously been tried unsuccessfully, we recommend using the program for moderate fatigue.
- **Moderate fatigue:** We recommend continuation of household and limited community activities that have been tolerated. Patients should begin an activity or aerobic exercise program with exertion at submaximal levels, RPE 9–11/Very Light-Light. The activity or exercise can then be slowly advanced as the patient tolerates as long as it does not cause worsening of symptoms (which may be delayed until the evening and/or days after the activity/exercise session). If symptoms worsen, activity should be returned to the previously tolerated level. Consider referral to a rehabilitation therapist with knowledge of post-COVID care to guide an individually titrated, symptom-guided program.
- **Severe fatigue or significant PEM:** Continue any household activities that have been tolerated without symptom exacerbation. Patients can begin a physical activity program, which should initially consist of upper and lower extremity stretching and light muscle strengthening before any targeted aerobic activity. Once tolerated, patients can begin an activity or aerobic exercise program at submaximal levels, RPE 7–9/Extremely to Very Light. The activity or exercise can then be slowly advanced as the patient tolerates as long as it does not cause worsening of symptoms (which may be delayed until the evening and/or days after the activity/exercise session). If symptoms worsen, activity should be returned to the previously tolerated level. Consider referral to a physician with knowledge of post-COVID care (such as a physiatrist) to guide an individualized

**TABLE 4** PASC fatigue treatment recommendations

#	Statement
1	Begin an individualized and structured, titrated return to activity program.
2	Discuss energy conservation strategies.
3	Encourage a healthy dietary pattern and hydration.
4	Treat, in collaboration with appropriate specialists, underlying medical conditions, such as pain, insomnia/sleep disorders (including poor sleep hygiene), and mood issues that may be contributing to fatigue.

Abbreviation: PASC, postacute sequelae of SARS-CoV-2 infection.

rehabilitation program that may require starting with a home health program for patients with very limited tolerance of community activities.

## Energy conservation strategies

We also recommend educating patients on energy conservation strategies to aid in recovery. One framework is the “Four Ps”: Pacing, Prioritizing, Positioning, and Planning.<sup>23</sup>

Pacing is the concept of avoiding the push and crash cycle that is common in post-COVID recovery. Ways to achieve optimal pacing include keeping activity to reasonable, and often shorter, durations (or alternatively, giving more time to complete activities to avoid rushing) and including scheduled rest breaks with activities. Patients should pay attention to their body and avoid or moderate activities that lead to the need for prolonged recovery periods.

Prioritizing encourages a patient to focus and decide on which activities need to get done on specific days and which activities can be postponed (or are unnecessary to do at all) to avoid overexertion and crashing.

Positioning is modifying activities to make them easier to perform. For example, it may be possible for the patient to sit during an activity or have a workspace at a comfortable height with all necessary equipment within easy reach. Another example would be the use of a shower chair or bench rather than standing for showering.

Planning encourages the patient to plan the day or week to avoid overexertion and to recognize energy windows. Energy windows are periods during the day when patients have more energy to complete tasks. Patients are often aware of their optimal energy window, which may vary throughout the week. Asking patients to keep a diary of good days, bad days, and energy windows is helpful for optimizing timing of therapy and activities. As such, it is important for patients to plan rest breaks. Other elements of planning include determining steps for completion of tasks and preparing for tasks ahead of time. Daily routines may also be helpful. Finally, planning may consist of gradual return to previous activities.

In particular, returning to work may be of concern to individuals with PASC-related fatigue. We recommend patients work with their physicians and employers to create a specific plan for return to vocational activities. Patients should be advised on ways to resume work, even if accommodations are needed or in a limited capacity as long as it does not worsen symptoms or lead to significant PEM. Examples of possible accommodations include working a limited number of hours, working from home, adjusting work activities (eg, seated instead of standing/walking activities), using durable medical equipment (eg, mobility aid to increase

walking tolerance), providing additional breaks throughout the day, and adjusting the work environment (eg, allowing the patient to park closer). These activities and return to work should be advanced as the patient tolerates. When available, referral to vocational rehabilitation counselor can be helpful in structuring the return activities and communicating with employers.

## Encourage patients to follow a healthy dietary pattern and stay hydrated throughout the day

At this time there are no scientific data to support the “prescription” of one specific diet for the management of PASC-related fatigue. General nutritional recommendations should reflect the individual patient’s underlying comprehensive health profile. General nutrition guidelines suggest a diet including vegetables, fruits, whole grains, healthy fats, fish, poultry, beans and eggs, dairy, and limited intake of red meats. Adequate intake of water and the avoidance of alcohol is also recommended.

Acute symptomatic COVID-19 is associated with a vigorous immune response and PASC has been theorized to be related to persistence of this immune dysregulation. There has been significant interest in the link between proinflammatory states and chronic disease related fatigue. Single nutrients (polyunsaturated fatty acids, antioxidative vitamins [specifically vitamins A, B12, and D], polyphenols, protein/amino acids) and specific diets (whole grains high in fibers, polyphenol-rich vegetables, and omega-3 fatty acid-rich foods) have been suggested to have anti-inflammatory and fatigue-reducing effects, although further confirmatory research is needed.<sup>24</sup>

Mast cell activation syndrome with histamine release has also been suggested to play a role in PASC related-fatigue.<sup>25</sup> It is proposed that some individuals may not tolerate histamine present in foods, thought to be a result of reduced activity of the enzyme diamine oxidase, which breaks down histamine leading to an increased amount of histamine in the body and histamine intolerance. Symptoms include headache, asthma, runny or blocked nose, low blood pressure, irregular heartbeat, hives, itching, diarrhea, flushing, and other conditions and are similar to those reported by individuals with PASC. Although there are no current scientific studies supporting the benefit of a low histamine diet (often consisting of limited cheeses, fruit, seafood, nuts, and other foods) in PASC, anecdotal reports have suggested improvement in some individuals. It is worth noting that challenges following low-histamine diets have also been reported.

Some dietary recommendations have been made for individuals with ME/CFS, and similar dietary recommendations may be beneficial for PASC-related fatigue. These include eating little but often - every 3 to 4 hours,

eating foods with a low glycemic index (more complex carbohydrates) in order to support stable energy levels, and eating a balanced diet including fruit, vegetables, fish, meat, dairy, nuts, beans, and pulses (eg, legumes). There is currently not sufficient evidence to support the use of specific nutritional supplements to help CFS including multivitamins, B vitamins, magnesium, essential fatty acids (omega-3s), carnitine, or coenzyme Q10.

Fatigue related to autonomic dysfunction in individuals with PASC, specifically postural orthostatic tachycardia syndrome (POTS), can be partially addressed with adequate water and salt intake.<sup>26,27</sup> Small and frequent meals are better tolerated and diets<sup>26</sup> with high fiber and complex carbohydrates may help reduce blood glucose (sugar) spikes and lessen POTS symptoms.

Fatigue due to muscle atrophy in the context of weight loss is reported in PASC and can be improved with appropriate caloric and protein intake.

## Pharmacologic therapy and supplements

There is a wide variation in the use of medications, herbal remedies and supplements to improve PASC-related fatigue. Some PASC-collaborative clinics do not use pharmacologic agents whereas others use agents when conservative management has been tried and comorbid conditions have been addressed. Further, patients often express interest in and desire for medications and herbal remedies/supplements that may be helpful so knowledge of these agents is needed for appropriate patient counseling.

Supplements that have been suggested to alleviate chronic fatigue in other causes of chronic illness (eg, multiple sclerosis, fibromyalgia, and ME/CFS) include branched-chain amino acids, omega 3 fatty acids, vitamin B12, vitamin C, vitamin D, magnesium, L-carnitine, coenzyme Q10, ginseng, echinacea, and many others.<sup>28-30</sup> These supplements have been suggested to support the immune system, reduce inflammation, help with healing, and improve fatigue. It is important to note that there was no consensus on the use of these supplements and they should be considered on a case-by-case basis, recognizing the limited scientific evidence. Additionally, there needs to be consideration of the out-of-pocket cost of supplements, the risk of medication interactions, lack of regulation, and possible side effects.

There are several medications that are commonly used for fatigue in other populations (eg, individuals with ME/CFS, cancer, multiple sclerosis, brain injury, and Parkinson disease) that some PASC clinics prescribe for PASC-related fatigue.<sup>31-34</sup> Specifically, amantadine, modafinil, and methylphenidate have been used by PASC clinics for the treatment of fatigue.<sup>35-38</sup>

Other medications that have been suggested in the treatment of ME/CFS include antivirals/antibiotics/antiparasitics, antidepressants, cytokine inhibitors, galantamine, glucocorticoid steroids, immunoglobulins, and rituximab.<sup>39-41</sup> Controlled trials are limited and evidence for these interventions does not exist or is inconclusive. Some of these medications have approval from the Food and Drug Administration for use in other populations with fatigue, but there are currently no clinical trials examining their use in the PASC population. It is important to note that none of these medications were recommended through our consensus process and therefore, should be considered on a case-by-case basis. There also can be adverse side effects and medication interactions with each of these medications that need to be considered prior to prescribing.

## Other therapies

The use of acupuncture has also been reported by collaborative patient representative members to improve fatigue. Although there has not been direct evidence to support its use in PASC-related fatigue, there is some preliminary low-quality evidence that supports its use in ME/CFS.<sup>42</sup>

## Health equity

In the context of PASC, it is important to focus on health equity, health disparities, and social determinants of health (SDOH). Along with the following discussion, clinicians are encouraged to reference the Appendix Table: Health Equity Considerations and Examples in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): Fatigue for guidance about the integration of health equity considerations with the evaluation and treatment of individuals with PASC.

The World Health Organization defines *health equity* as “the absence of unfair and avoidable or remediable differences in health among population groups defined socially, economically, demographically or geographically.”<sup>43</sup> Healthy People 2020 defined a *health disparity* as “a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage” and stated that health disparities “adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.”<sup>44</sup>

There has recently been an increased awareness of how SDOH are contributing to health inequities and

disparities. SDOH are the “nonmedical factors that influence health outcomes” and involve the “conditions in which people are born, grow, work, live, and age and the wider set of forces and systems shaping the conditions of daily life.”<sup>45</sup> For example, the forces and systems can include economic policies, government agendas, and social norms. From an individual’s perspective, SDOH includes level of education, socioeconomic status, employment, neighborhood safety and access to nutritious food, and other factors.

To promote high-quality care in individuals with PASC, we need to ensure resources are equitably available for those affected to maintain physical and mental health. Examples of resources include access to information (eg, written and/or oral in a language the individual easily understands or adapted for someone with a disability), goods and services, affordable and timely testing and care, and medical and mental health care that are all tailored to meet the individualized needs of people, especially those from marginalized communities. When policies, programs, and systems that support health are equitable, poor health outcomes can be reduced, health disparities can be prevented, and the whole of society benefits.

Whereas the association between race/ethnicity and health inequity in acute COVID-19 is now well established, the association of inequities with PASC is relatively unexplored.<sup>46</sup> As more data emerge, there will likely be evidence of racial/ethnic health disparities in accessing care and treatment options because of differential loss of health insurance, inequitable distribution of testing, limited clinical and hospital resources, lack of Internet/broadband access, food insecurity, housing insecurity, and differences in work-related exposures.<sup>46</sup>

Symptoms of fatigue may be reported more commonly in female adults and in older age groups.<sup>24</sup> COVID-19 symptoms may be more severe in pregnant women<sup>47</sup> and pregnancy itself (and the postpartum period) is a well-known cause of fatigue because of a host of biologic and behavioral factors. In addition, people who identify with racial or ethnic minority groups may have a baseline level of chronic fatigue that should be considered in the assessment and treatment approach.<sup>48</sup>

Racial and ethnic minority groups may also be at a higher risk of chronic diseases that may increase baseline levels of chronic fatigue. For example, individuals with lower socioeconomic status, non-Hispanic Black adults, and Hispanic adults are at higher risk of obesity, which increases the risk of fatigue.<sup>46</sup> Higher body mass index and obesity are also related to more severe consequences of PASC.<sup>49</sup> Finally, those with lower socioeconomic status may not be able to access appropriate treatments. For example, they may not have the ability to get time off from work to apply appropriate pacing recommendations or to access therapy services.

Vulnerable populations encounter a range of barriers to health care linked to demographic and/or socioeconomic factors such as gender, race/ethnicity, education, occupation, and transport.<sup>50</sup> The structural and cultural divide between the academic health care systems and underrepresented minority communities must be bridged by trusted sources that, in many cases, are community organizations. Community organizations that are faith based, nonprofit, civic, social support related, or education focused serve as the foundation of community engagement.<sup>51</sup>

Strategies that are culturally appropriate and community competent and consider the nuances of population, community, family, and individual differences have a vital role in reducing health disparities, promoting health equity, and improving population health. Such approaches require a deep understanding of community, consideration of local data-driven approaches, diverse and equitable partnerships across sectors, messaging that resonates with the target audience(s), and the implementation of policies that support the health of all individuals in the United States.<sup>52</sup>

Vulnerable populations facing PASC may have little or no health insurance coverage. In addition, debilitating and disabling symptoms interfere with people’s ability to work and therefore to generate income for themselves and their dependents. The vulnerable in society have less job security, less flexibility in their roles, and less entitlement to sick pay and occupational health services.<sup>53</sup>

To address inequities in care delivery, we recommend assessment and treatment approaches that incorporate telemedicine, including phone calls and virtual visits, as they can be helpful for ongoing follow-up and might lessen the burden on individuals with limited energy from PASC or who have other concerns about in-person visits (eg, the cost of travel, parking, facility fee charges). Virtual visits expanded rapidly during the pandemic and have been noted to be useful in closing access gaps for various populations such as ethnic/racial minority groups, rural communities, and the elderly.<sup>54</sup> In addition, individuals should be connected to appropriate social services when available, including assistance for other hardships (eg, financial, family illness, bereavement, caregiving) and resources on disability and reasonable accommodations for work or school, and connections to PASC support groups.

## **FUTURE DIRECTIONS IN ASSESSING AND TREATING PASC-RELATED FATIGUE**

PASC-related fatigue affects individuals physically, emotionally, and cognitively. Individuals with PASC-related fatigue can experience severe disability and frustration. The pathophysiology causing fatigue after COVID-19 still warrants ongoing detailed research to

better understand this constellation of symptoms, while acknowledging the cause of fatigue is likely multifactorial and may be specific to the individual. The goal of this PASC Collaborative Consensus Guidance Statement is to create a coordinated and systematic approach to the evaluation and treatment of patients presenting with PASC. The recommendations represent a consensus of large national multidisciplinary collaborative of centers focused on the treatment of individuals with PASC. The recommendations are based on the most current available data, extrapolation from evidence in similar conditions, and the combined clinical experience of treating thousands of patients with PASC-related fatigue.

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## APPENDIX

### Health equity considerations and examples in post-acute sequelae of SARS-CoV-2 infection (PASC): Fatigue

Category	Comment	What is known	Clinical considerations
<b>Biologic gender</b> <i>Example: Pregnant women</i>	Physiologic and biologic gender differences should be considered for both the diagnosis and treatment of PASC-related fatigue.	Pregnant women frequently have pregnancy-related fatigue, and they may be at higher risk for more severe COVID-19 infections and symptoms, particularly women who have certain comorbidities and other characteristics (eg, older age, diabetes, kidney disease, obesity). <sup>HE-F-1</sup>	Pregnant women who are status post COVID-19 infections may experience pregnancy-related fatigue in addition to PASC-related fatigue and may need alternatives to diagnostic testing (eg, radiation exposure) to avoid potential harm to the fetus. The risks and benefits of medications and other treatment interventions should be assessed for both mother and fetus. Exercise prescriptions may be affected by symptoms such as excessive vomiting and weight loss in the first trimester and large girth, back pain, or preeclampsia in the third trimester.
<b>Gender</b> <i>Example: Transgender individuals</i>	People across the gender spectrum may have unique health issues.	Gender-affirming medical interventions such as hormonal therapy or surgery may affect fatigue, strength, and endurance. Many individuals had challenges accessing gender-affirming care during the pandemic, and this may be related to an increase in sleep disorders and mental health symptoms <sup>HE-F-2</sup> and/or delays in elective surgery.	In the context of rehabilitation for PASC-related fatigue, it is important to assess the current and planned future gender-affirming care for transgender patients. Hormonal status, sleep, and mental health should be prioritized as they may all affect fatigue. If elective surgeries are planned in the future, prehabilitation may help to increase strength and endurance and decrease psychological stress. <sup>HE-F-3</sup> Virtual visits may offer better access to care. <sup>HE-F-4, HE-F-5</sup>
<b>Racial/Ethnic Minority Groups</b> <i>Example: People who identify as Black (including African-</i>	BIPOC (Black, Indigenous and People of Color) communities have been especially affected	Social determinants of health, societal factors and structural racism have disproportionate	PASC-related fatigue is multifactorial, with its effects compounded for individuals

(Continues)

Category	Comment	What is known	Clinical considerations
<p><i>American), American-Indian/ Alaska Native, Pacific Islander, Asian-American, and Mixed Race, and/or Latino/Hispanic (ethnicity)</i></p>	<p>by the global pandemic. As result, these groups have worse outcomes after COVID-19 infection, including hospitalizations, morbidity, and mortality.<sup>HE-F-6</sup></p>	<p>effects on underinvested communities.<sup>HE-F-7,HE-F-8,HE-F-9</sup> Statistical models that control for susceptibility, exposure, and health care access reveal no disparity or the degree of the disparity is decreased in multiple studies; thereby demonstrating that exposure-related factors are contributing more to disparities than biological susceptibility.<sup>HE-F-6</sup></p>	<p>already under the burden of racial and ethnic disparities and injustice. Standardized treatment and management protocols may help decrease implicit bias from providers to patients from racial and ethnic minority groups.<sup>HE-F-10</sup> In treating fatigue, antiracist awareness of these issues may require a multidisciplinary approach to health care, including but not limited to addressing low-cost health care, food/housing insecurity, health literacy with access to low-cost information, access to transportation, obtaining or maintaining employment. Where appropriate, consider providing documentation to support food vouchers, housing assistance, transportation/vehicle parking pass, temporary workplace accommodations, and neighborhood support network. Local and national advocacy is needed to address ongoing systemic inequities.</p>
<p><b>Justice Involved (Prisons/ Detention Centers)</b>  <i>Example: People who are incarcerated or detained in prisons, jails, youth detention centers, immigration detention centers, internment camps and other facilities</i></p>	<p>People who are involved in some manner with various aspects of the criminal justice system, particularly those who are incarcerated in correctional facilities and detention centers, have a unique vulnerability to healthcare inequity that is often overlooked.</p>	<p>There have been high rates of COVID-19 infection in U.S. prisons, and this affects not only the health of incarcerated individuals but also the employees, and their families and communities.<sup>HE-F-11</sup> The public health implications of these facilities should encourage clinicians and policymakers to consider the public health concerns posed by these facilities when developing pandemic-response policy. Incarcerated people have high levels of co-morbid conditions including other infectious diseases such as HIV/AIDS, hepatitis C virus and tuberculosis.<sup>HE-F-12,HE-F-13</sup> They are also at risk for chronic diseases (eg, hypertension, diabetes) and are at risk for worse health outcomes. They have a disproportional burden of substance use disorders and mental health illnesses.<sup>HE-F-12,HE-F-13</sup></p>	<p>Public health measures should include modifications to general community recommendations that will adequately address the special needs of this population. Social distancing, quarantine upon exposure, and separate bathrooms may not be possible and/or may unintentionally cause physical or emotional distress, possibly worsened by PASC-related fatigue. Early and continual access to high-quality physical and mental health care may be optimized through telehealth, personalized fatigue management strategies, and outcomes accountability for the facility staff. Clinicians should be aware of the health disparities in the context of social determinants of health that lead to a disproportion of racial and ethnic minorities within the criminal justice system.<sup>HE-F-13</sup></p>
<p><b>Disability</b>  <i>Example: People who have impairments in physical</i></p>	<p>Health care and society in general make assumptions, foster unconscious bias (that include</p>	<p>Before the COVID-19 pandemic, people with disabilities were marginalized, enduring</p>	<p>As a group, many individuals with PASC-related fatigue advocate for treatment,</p>

(Continues)

Category	Comment	What is known	Clinical considerations
<p><i>mobility, psychological/mental health, vision, hearing, emotional/social relationships, cognitive/learning, speech and communication, and other disabilities</i></p>	<p>stereotypes) toward people with disabilities; the consequences lead to devaluation and disparate treatment of people with disabilities.<sup>HE-F-14</sup></p>	<p>reduced access to community resources, physical and emotional barriers to social services, and decreased access to high-quality health care.<sup>HE-F-15</sup> During the pandemic, community participation was further impaired by necessary public health mandates such as travel restrictions, social distancing, and wearing a face mask that did not allow lip reading.</p>	<p>funding, and research as a chronic disability.</p> <p>The federal government has several laws established to protect the rights of disabled persons.<sup>HE-F-16</sup> Clinicians should familiarize themselves with the Americans with Disabilities Act (ADA), a civil rights law that guarantees equal access and prevents discrimination in areas of social life (health care coverage, employment, transportation, state and local government services, telecommunication, school, etc.). The Rehabilitation Act of 1973 (Rehab Act) protects equal access for individuals with disabilities through the removal of architectural, employment, and transportation barriers for organizations that receive federal assistance.</p> <p>When appropriate, clinicians should advocate for patients with PASC-related fatigue to obtain disability insurance, a home health aide, durable medical equipment (eg, hospital bed, mobility aids, communication devices) workplace/school modifications (eg, classroom or workplace adaptations, accommodations for lectures, notes and test-taking, learning aids/special education resources, modified schedule), or an emotional support animal.</p> <p>Strategies for information dissemination should include options for those who are visual, hearing, communication and learning impaired. Although telemedicine has augmented access for many who are mobility impaired, clinicians must consider telemedicine options such as telephone calls for those who do not have access to smart phones, consistent Internet broadband access or the knowledge to operate video telecommunication.</p>
<p><b>Immigration</b> <i>Example: People who have come from another country</i></p>	<p>Immigration-related issues may pose numerous barriers to health and health care for many individuals.</p>	<p>Many health inequity issues in immigrant communities in the United States during the COVID-19 pandemic are well</p>	<p>Regarding PASC-related fatigue, both the diagnostic work up and treatment may take place in the context of patients</p>

(Continues)

Category	Comment	What is known	Clinical considerations
<i>in order to live in the United States</i>		documented (eg, high rates of acute infections, more severe disease, worse outcomes).	being underinsured or uninsured, having physically demanding jobs, difficulty taking time off from work for financial reasons, and living in close quarters that may disrupt sleep. Some of the solutions to care that have been documented in the literature include engaging community leaders, providing virtual patient navigators, using language-appropriate educational materials, and offering free legal assistance to access resources. <sup>HE-F-17</sup>
<b>Religion</b> <i>Example: People who identify with a shared belief in what is sacred, holy, divine, spiritual, or reverent</i>	Religion based practices deserve special consideration during healthcare evaluation.	Physical and psychological factors that influence fatigue (eg, disfavoring transfusion of whole blood product for severe anemia, <sup>HE-F-18</sup> modesty <sup>HE-F-19</sup> in communication about sensitive topics, or moral injury <sup>HE-F-20</sup> during a global pandemic) can affect those committed to various religious practices.	For individuals with PASC-related fatigue, religious practices such as fasting may increase symptoms. Fasting might also reduce physical activity <sup>HE-F-21</sup> and affect conditioning and/or ability to participate in rehabilitation therapies. Although certain nutritional supplements, <sup>HE-F-22</sup> natural remedies, <sup>HE-F-23</sup> and faith-based practices may have varying potential for anti-inflammatory or antioxidant properties to treat fatigue, clinical decisions regarding their use for PASC-related fatigue should ideally be considered in conjunction with an experienced professional and if deemed safe should be used in a complementary manner with evidence-based therapies.

Legend: This table is included in the Appendix to provide additional information for clinicians who are treating patients for PASC-related fatigue. This is not intended to be a comprehensive list, but rather to provide clinical examples as they relate to health equity, health disparities, and social determinants of health. The literature demonstrates that all marginalized groups face socioeconomic barriers and access to care barriers, though these may or may not be barriers for a specific individual patient. People with intersectional identities (eg, those who identify with more than one underrepresented or marginalized group), often face enhanced levels of bias and discrimination.

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